DEPRESSION: AN OVERVIEW IN THE PATHOPHYSIOLOGY AND TREATMENT

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Abstract: Depression is a potentially life-threatening disorder in worldwide. Depression a mental health disorder characterized by persistent depressed mood or loss of interest in activities, causing daily life to be significantly impaired. Deprivation of glucose in energy metabolism of brain leads to depression. To overcome this reduction of glucose in brain, lactate is significantly impaired with energy metabolism of brain. Monocarboxylate transporters [MCTs] have a high capacity for transporting short-chain monocarboxylates, such as lactate, Pyruvate and the ketone bodies through blood brain barriers. MCT1, MCT2, and MCT 4 have contributed to the emergence of the physiological concept of intercellular lactate shuttle. Lactate shuttle sources of distress include potential triggers. Increasingly, activation of certain neural circuits in the brain can trigger changes in brain function. . This hypothesis can help to elucidate the surprisingly positive results found in the treatment of depression with lactate shuttle. Psychological and pharmacological therapy, or a mixture of both, is typically the primary basis of treatment. Research is increasingly suggesting that these treatments can normalise depression-related brain changes.

Keywords: Depression, monocarboxylate transporters (MCTs), Lactate shuttle.

I. INTRODUCTION:

Depression is a major infirmity characterized by an inability to carry out daily activities of an individual usually enjoys and continual sadness habitually accompanied by the loss of interest in activities [1] In worldwide depression is the predominant component and one of the top three illness of disease burden ‘cause and effect 'of depression have relationship with many non-communicable diseases (NCDs) [2]. Depression occurs nearly twice as much in women as in men [3] and affects approximately 6 % of the world's adult population every year[4] The share of the global population suffering from depression in 2015 was projected to be 4.4 %, according to the World Health Organization (WHO) [4]. Furthermore, depression is associated with an elevated risk of developing conditions such as diabetes mellitus, heart disease and stroke [5], thus increasing its disease burden further. In addition, depression can lead to suicidal death. [6]

Genetic, epigenetic, physiological, and psychosocial factors are commonly implicated in the biological basis of mood disorders [7]. Depression may be associated with genes that occupy a fixed location on chromosome 8, 15 and 17, according to some studies [8]. A particular mechanism comprising multiple malfunctioning neural circuits [9] may actually linked to neurotransmission disorders in the brain, including substances such as serotonin , norepinephrine, dopamine, gamma-aminobutyric acid (GABA), cerebral nerve growth factor (BDNF) [10].

Glucose is the brain's primary source of energy [11]. Decreased brain energy metabolism is linked to cognitive dysfunction in depressive disorders [12]. Lactate has long been thought to be a glycolytic by-product in the brain [13] but lactate has been transposted to the brain by monocarboxylate transporters (MCT). MCTs are a protein family with 14 different isoforms. MCT1-MCT4 transports astrocytes from lactate, pyruvate, and ketone bodies to gial cells [14]. Lactate, on the other hand, is an essential energy substrate that plays an important role in the metabolism and development of energy memory, according to growing evidence [13]

Fortunately, our view about pathophysiology, treatment, and the biochemical basis of depression and the role of monocarboxylates for sustaining brain functions has changed in depression, bringing new attention on monocarboxylates and their transporters MCTs mediate the release of lactate from astroycytes and its incorporation into neurons, which could generate satiety during deperession.

II. SIGNS AND SYMPTOMS OF DEPRESSION [15]

Depression varies from person to person, but certain signs and symptoms are typical. It's important to bear in mind that these signs may be part of the usual lows of life. However, the more symptoms a depressed person has, the worse they are and the longer they last, the more likely they are to struggle with depression.

2.1 Common symptoms of depression

- **Feelings of helplessness and hopelessness**
- **Loss of interest in daily activities**
- **Appetite or weight changes**
- **Sleep changes**
- **Anger or irritability**
- **Loss of energy**
- **Self-loathing**
- **Reckless behavior**
- **Concentration problems**
- **Unexplained aches and pains**
- **Suicidal thoughts or attempts**

Symptoms must last for a minimum of two weeks and reflect an improvement in the previous level of functioning for depression diagnosis. Medical conditions can also mimic symptoms of depression (e.g., thyroid problems, a brain tumour or vitamin deficiency), so it is important to rule out general medical causes. [16].

III. TYPES OF DEPRESSION

Major depression, Persistent depressive disorder [formerly known as dysthymia], bipolar disorder, and seasonal affective disorder are the four most common forms of depression [17].

3.1 Major depression: MDD [Major depressive disorder] is often associated with comorbid mental and medical problems, and it is coupled with a high risk of mortality and morbidity [18]. Traditionally, studies into the neurobiology of MDD has centered on the monoamine neurotransmitters norepinephrine and serotonin. The monoamine hypothesis proposed that depressed people are more possible to have low levels of these neurotransmitters because antidepressant drugs increase their levels acutely [19].

3.2. Persistent depressive disorder: This type of depression, formerly known as "dysthymia," is defined as a persistently low mood that lasts at least two years but does not progress to severe depression. Chronic depressive disorder [PDD] is characterized by changes in appetite and sleep patterns, as well as low appetite, low self-esteem, and hopelessness. [17]

3.3. Bipolar disorder: Manic Depressive Illness-MDI [Bipolar Affective Disorder] is a common, severe, and long-term mental illness [20]. This is a serious condition that will affect you for the rest of your life. Periods of deep, extended, and intense depression alternate with periods of excessively elevated mood known as mania in MDI. Just one manic/hypomanic episode is needed to be diagnosed with bipolar disorder rather than unipolar disorder [21].

3.4. Seasonal affective disorder (SAD): This type of depression occurs as the days get shorter in the fall and winter. Changes in the body's normal daily rhythms, the sensitivity of the eyes to light, or the action of chemical messengers like serotonin and melatonin can all cause mood swings. The most common treatment is light therapy, which entails sitting in front of a particularly bright light source on a regular basis.

3.5. Depression types unique to women

3.5.1. **Perinatal depression:** This kind of depression involves major and minor depressive symptoms (also known as postpartum depression) that occur during pregnancy or in the first 12 months after delivery. Up to one in seven women who give birth are affected by perinatal depression [22].

3.5.2**. PMDD**: A serious kind of premenstrual syndrome, or PMS, is this kind of depression. PMDD symptoms usually begin shortly after ovulation and cease once menstruation begins. Symptoms can be reduced by selective serotonin reuptake (SSRI) inhibitors, such as fluoxetine [Prozac] and sertraline (Zoloft) [23].

IV BIOCHEMICAL BASIS OF DEPRESSION

Neuroanatomy and electrophysiology were introduced at the beginning of the 20th century. Neuroscience is an interdisciplinary field packed with areas ranging from cell and gene function molecular studies, biological investigations, behaviour-regulating cellular and molecular machinery [34].

4.1 Synaptic transmission

In order to synthesis neurotransmitters, synaptic transmission needs several measures. The accumulation of the neurotransmitter in the secretary vesicles and the control of the neurotransmitter and the release into the synaptic cleft between the pre- and postsynaptic neurons, as well as the termination of the action of the neurotransmitter and the activation of the final cellular response via the various signal transduction measures.

The synaptic transmission was terminated by the transmitter binding to particular proteins of the transporter and the presynapse reuptake. The enzymes such as monoamine oxidase (MAO) that are stored in the vesicles again promote this process [25].

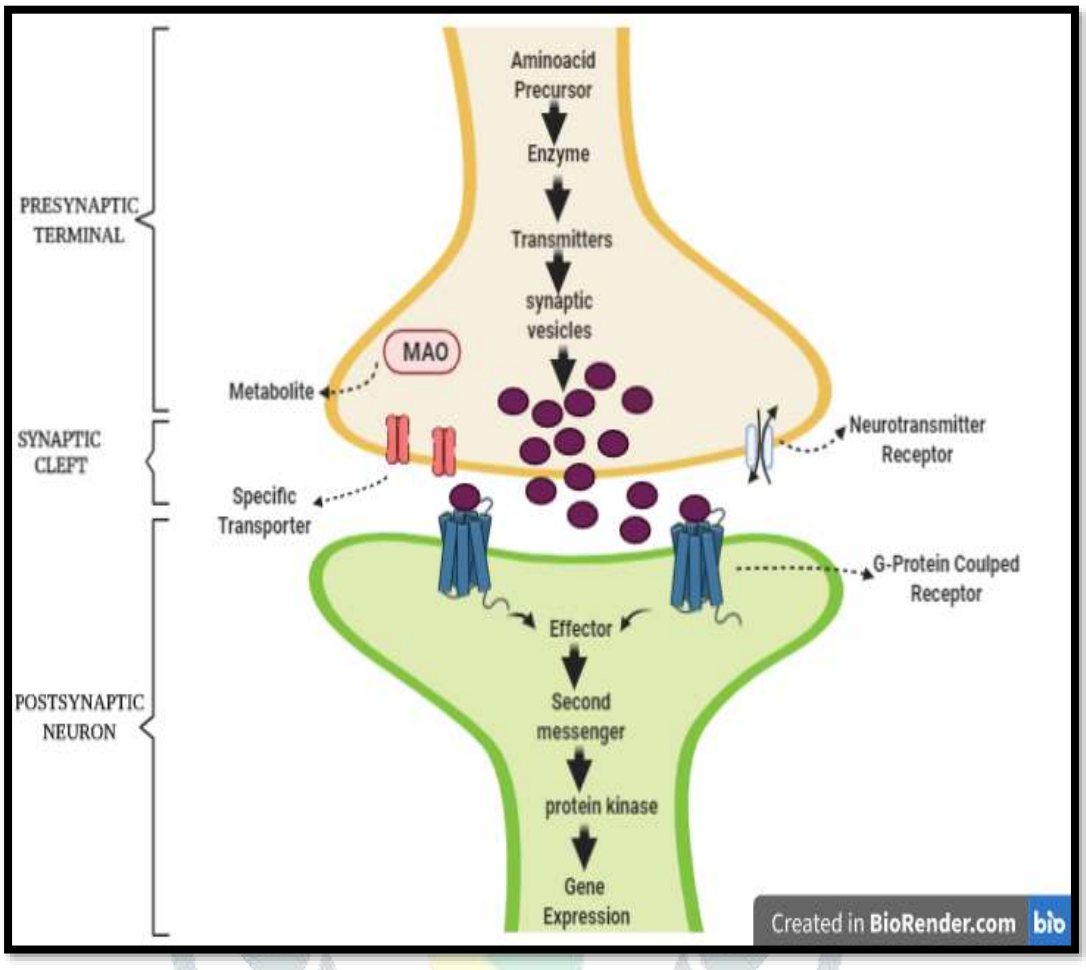

Figure 1. Synaptic transmission

Figure 1 displays the synapse's schematic representation and the chemical transmission measures. The aminoacid precursors are transferred from the blood to the brain in the initial process. The precursor transforms the enzymatic reactions into the transmitters. The transmitters are stored by a Ca^{2+} based reaction in the synaptic vesicles that are released into the synaptic cleft. Then, to control synthesis and release, the neurotransmitters are rich in neurotransmitter receptors. The transmitters are released from the presynaptic autoreceptor into the postsynaptic receptors by the downstream signal transduction cascade, whereby the signals are transducted.

Through initial binding of neurotransmitter molecules to the post-synaptic membrane of the surface receptor, which are also coupled to guanine nucleotide binding proteins (G-Protein), neurotransmitter compounds do not cross the postsynaptic membrane but establish a cascade of response. A variety of successful mechanisms in cells, including second messengers such as adenylcyclases, phospholipases and phosphoinositide mediated mechanisms, are modulated by these G-proteins [26]. These second messengers, improved by the cascade of signal transduction, initiate a pathway through phosphorylation of protein kinase [24]. A key mechanism underlying depression may be the altered activity in one or more stages of this synaptic transmission. This process was an instrument for determining the action of the antidepressant.

4.2. Monoamine hypothesis

The theory of monoamine shows the main signs and symptoms of depression due to a functional deficit of monoaminergic transmitters such as nor-epinephrine (NE), serotonin (5-HT), dopamine, whereas vital synapses may induce mania in the brain due to functional overload of monoamines. The monoamine theory indicated that the antihypertensive medication, such as Reserpine, induces nor-epinephrine, serotonin, dopamine, which contributes to depression, to deplete presynaptic stores. Euphoria and hyperactive behaviour can be encountered by patients treated with Iproniazid. The Ipronizid compound inhibits the MAO metabolic enzyme. This inhibition increases the concentration of NE and 5-HT levels [27].

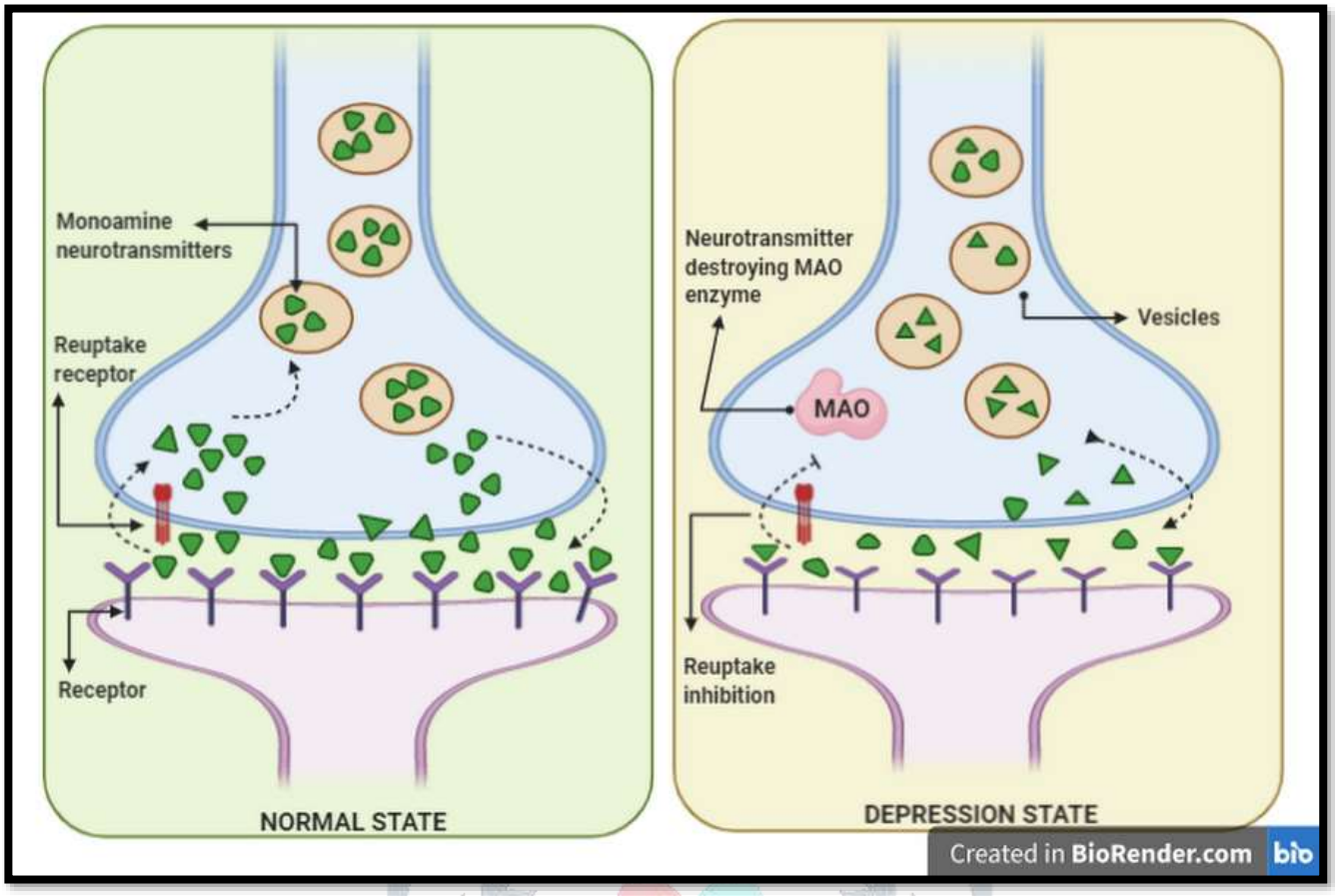

Figure 2. Monoamine hypothesis

The origin of the brain's Dopaminergic, Serotogenic, Noradrenergic neurons and their projections in many areas of the brain makes it clear that many behavioural processes, such as retardation, exhaustion, motivation, vigilance, mood, are responsible for monoaminergic processes. The distorted synthesis, storage or liberate of the functions of the neurotransmitter and subcellular messenger can contribute to the development of the manic condition and abnormal function and behavioural consequences of depression [24].

4.3. Depression as a Neurodegenerative Disorder

Neurodegeneration is generally referred to as the progressive defeat of working neurons, often associated with structural and neuro-morphological changes [28]. Psychiatric and mood changes are division of the clinical presentation of these neurodegenerative diseases, along with depression [29]. Brain disorders or imbalances, specifically serotonin, norepinephrine, and dopamine neurotransmitters, have been correlated with depression. Reduced hippocampal volumes were found to contribute to the hypothesis that chronic stress would inhibit neurogenesis in a series of experiments in humans subjected to chronic stress, retracting dendritic processes leading to hippocampal neuronal loss [30]. Brain-derived neurotrophic factor (BDNF) regulates synaptic plasticity in neuronal networks involved in depressive behaviours [31]. Upregulation of BDNF may reverse stress-induced structural and synaptic plasticity deficits in the adult brain, resulting in cognitive resilience and an enhanced ability to respond to environmental challenges that may precipitate or aggravate depressive episodes. Recent studies have shown that BDNF levels in suicidal patients' blood are reduced and their levels are increased by antidepressant medication. Higher BDNF plasma levels have been correlated with better patient results, independent of the medication used. Furthermore, BDNF polymorphism and serum level have been associated with anxiety, risk of depression, neuroticism and serotonergic neurotransmission [32].

4.4. Role of Monocarboxylate Transporters in Depression

Monocarboxylate transporters (MCTs) constitute a family of 14 transmembrane proteins encoded by the SLC16A family of genes [33]. One of the major sub-groups of membrane proteins found in mammalian cells is the solute carrier (SLC) superfamily. Because of their essential function in the recovery of neurotransmitters such as GABA, glutamate, serotonin, dopamine, and noradrenaline and control of their concentration in synaptic regions, neurotransmitters are considered a pharmacological goal of neuropsychiatric drugs in solute carrier family neurons. As a result, solute carrier transporters play a significant and varied role in neurodegenerative diseases [34].

MCTs are present in a number of tissues, including the brain, where three isoforms have been identified: MCT1, MCT2, and MCT4. In the brain, each of these isoforms has a diverse regional and cellular distribution [35] MCT1 and MCT4, which are located in astrocytes, are known to take part in the preferential release of lactate, while MCT2, which is present in neurons, has been related to lactate intake [36]

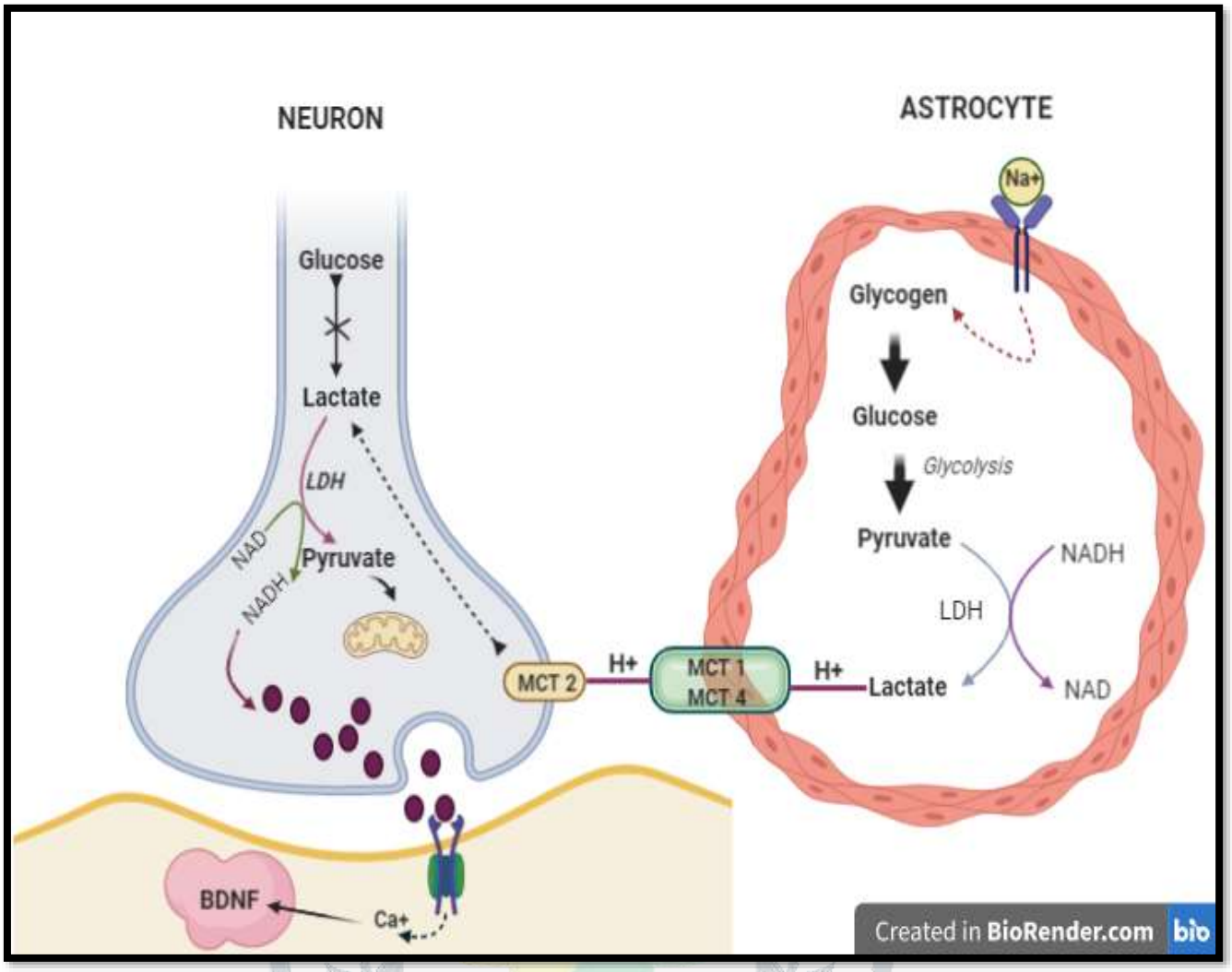

Figure 3. Role of MCT in depression

Physically, the brain requires high-energy metabolism to meet the energy needs of memory formation and consolidation [37]. Several studies have confirmed that decreased brain energy metabolism may precede and can contribute to neuropathogenesis leading to depression [38]. Mostly the brain's energy demand is supplied by glucose. Among the transport of monocarboxylates (MCT- monocarboxylic acid transporters) and hexose and pentose sugars [GLUT-glucose transporters] are predominantly essential for brain metabolism [39]. Additionally, monocarboxylates such as lactate, pyruvate and ketone bodies have been known for some time represent substantial energy substrates meant for the brain [40]. Through rapid transport of monocarboxylates across the plasma membrane of cells and blood brain barrier [41]. Monocarboxylates, especially lactate, which has long been regarded as a waste of cellular activity, plays a significant role in brain energy metabolism [42].

4.5. Astrocyte-Neuron-Lactate Shuttle Hypothesis

The brain's normal functioning and energy metabolism are dependent on neuro-glial interactions [43] Lactate may also be transported between astrocytes and neurons [44]. The astrocyte-neuron-lactate shuttle hypothesis describes this mechanism [ANLSH]. Both astrocytes and neurons demonstrating the ability to metabolize lactate, the ANLSH is responsible for up to 33% of the total energy substrate used by the brain [45]. Astrocytes metabolize glucose during exercise and produce lactate as a by-product. MCT4 facilitates lactate efflux from neurons by releasing lactate into the interstitial fluid.

Lactate is then transported into neurons through MCT2, where lactate dehydrogenase converts it to pyruvate enzymatically. Within astrocyte mitochondria, pyruvate ultimately reaches the citric acid cycle, leading to oxidative ATP yield [46]. It's worth remembering that neurons get lactate not just from astrocytes but also from the bloodstream [47]. Depending on the metabolic demands placed on neurons, this complex mechanism may allow astrocytes to switch between glucose and lactate shuttle mechanisms [48].

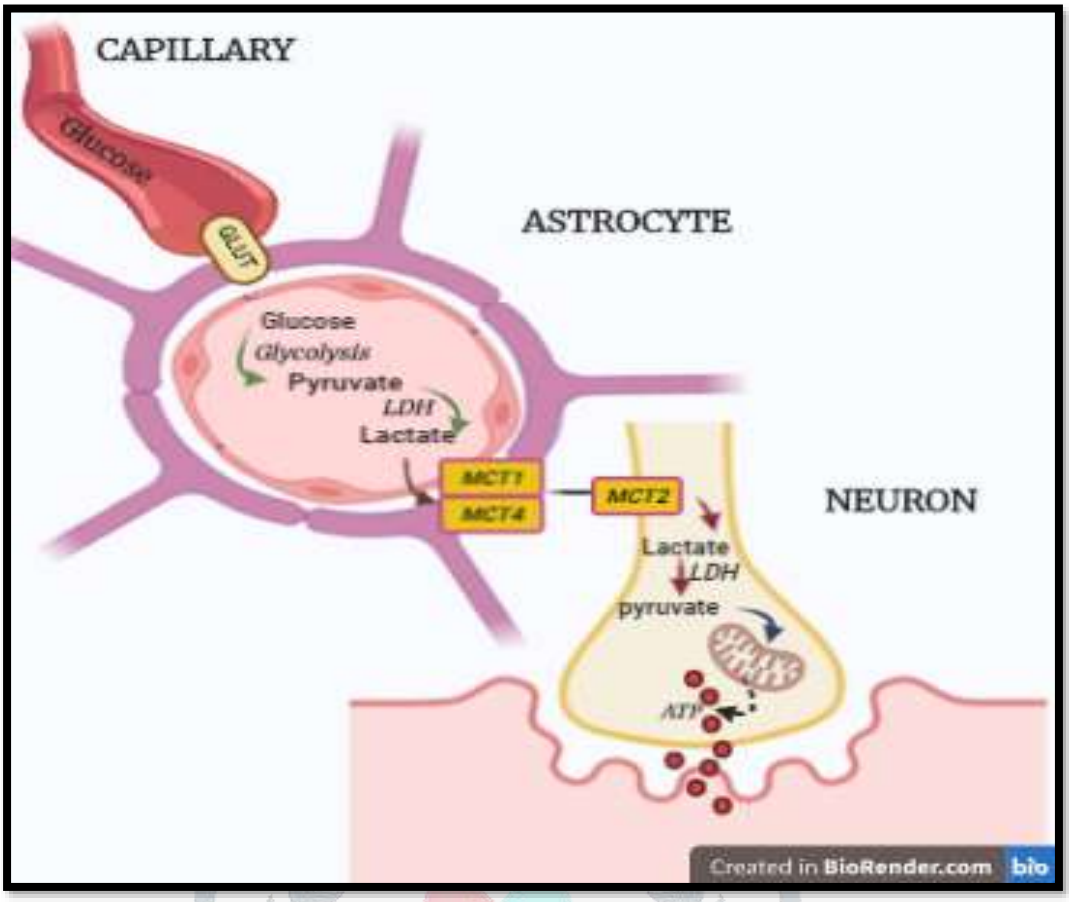

Figure 4. Astrocyte-Neuron-Lactate Shuttle Hypothesis

As a result, the ANLSH can be considered a useful mechanism for preserving optimum neuronal, astrocyte, and cognitive function [49]. Depression can promote lactate incorporation through the blood-brain barrier or release from glial cells, activating neurons [50]. The existing literature supports the role of MCTs in brain metabolism and treatment, which is significant in the context of depression.

V. TREATMENTS FOR DEPRESSION

a. Physical treatments
b. Psychological treatments
c. Self-help and alternative therapies

5.1. PHYSICAL TREATMENTS

5.1.1. Anti-depressants

Antidepressants are drugs that modify the chemical imbalances between neurotransmitters in the brain to help ease the symptoms of depression. Chemical imbalances cause mood and behavior changes [51]. Neurotransmitters including serotonin, dopamine, and noradrenaline or norepinephrine are released by one nerve's exonic end and obtained by the other, resulting in a phenomenon known as synergy [52] Antidepressants suppress neurotransmitter reuptake through particular receptors, resulting in an increase in the concentration of a specific neurotransmitter across nerves in the brain [53]. Antidepressants come in a number of ways and have varying degrees of effectiveness in the more biologically suicidal cases. Selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), and irreversible monoamine oxidase inhibitors (MAOIs) are three forms of antidepressants that influence multiple neurotransmitter pathways [54].

Selective serotonin-reuptake inhibitors (SSRIs) can block 5HT reuptake and increase synaptic 5HT transmission, according to Celada. The effect of SSRIs on the reuptake of other neurotransmitters is small or non-existent [55]. The muscarinic and histaminergic receptors are not activated by SSRIs, resulting in moderate anti-cholinergic (ACH) and sedative impact [56].

TCAs obstruct the release of norepinephrine (NE) and serotonin (5HT) [57]. This phenomenon, which is the primary mechanism of antidepressant action, triggers structural changes in neuro-receptors. TCAs have been shown to inhibit histaminic receptors, muscarinic and alpha1 adrenergic [58].

Antidepressants including monoamine oxidase inhibitors (MAOIs), phenelzine (Nardil), and tranylcypromine (Parnate) block the enzymatic synthesis of 5HT and NE into their metabolites [59]. MAOIs are used to treat atypical or drug-resistant depression in some situations. These compounds have a certain amount of toxicity. Moclobemide (manerix), on the other hand, has been described as the first reversible monoamine oxidase an inhibitor (RIMA). This molecule has been found to be more effective and healthy [60].

5.1.2. Mood stabilizers

Ionic shifts and changes in membrane permeability, according to historical perspectives, cause mood disturbances by causing direct impairments in neuronal excitability and transmission [61] Lithium carbonate, sodium valproate, and carbamazepine are the most commonly used mood stabilizers [62]. Lithium has been investigated for its effects on neurotransmitter chemistry in a variety of studies. Lithium has been shown to have effects on a number of neurotransmitter and neuromodulator processes, including monoaminergic, serotonergic, cholinergic, and GABAergic systems in early studies [63]. It's important to remember that even after getting better, people sometimes need to keep taking medication for a while to prevent a relapse [64].

5.1.3. Electroconvulsive Therapy (ECT)

In the ECT procedure, an electrical current is passed through the brain to induce controlled convulsions (seizures) [65]. ECT affects the expression and release of a wide range of neurochemicals in the brain, including transcription factors, neurotransmitters, neurotrophic factors, and hormones, as well as the mechanism of neurotransmission [66]. ECT operates on several levels during chemical neurotransmission, including neurotransmitter production, release, and binding of neurotransmitters to receptors, as well as their reuptake [67, 68]. It raises the concentration of a particular neurotransmitter in the brain's nerves [69]. ECT, which is also very effective, relieves depression in a number of people within one to two weeks of beginning treatment [70].

5.2. PSYCHOLOGICAL TREATMENTS

Psychiatric therapies for depression [71] and psychological interventions are successful in suicidal primary care patients, according to the UK National Institute for Health and Clinical Excellence (NICE) guidelines [72]. There are many forms of psychotherapy that can help suicidal people recover, including cognitive-behavioral, interpersonal, psychodynamic, and other types of "talk therapy" [73].

5.3. SELF-HELP AND ALTERNATIVE THERAPIES

Self-help and alternative therapies are unlikely to result in the more biological forms of depression when used alone [melancholic and psychotic depression]. However, such therapies can be helpful as an alternative to physical therapy [74]. Physical exercise has been recommended as a complementary treatment that can help to improve residual symptoms of depression and prevent relapse [75].

A systematic review of the antidepressant effect of exercise therapy was published in the British Medical Journal in 2001 [76]. The monoamine hypothesis of depression suggested that the monoamine neurotransmitters serotonin and norepinephrine were insufficiently accessible. Serotonin and norepinephrine levels rise as a result of exercise [77].

Physical activity has been shown to enhance serotonin neurotransmission, strengthen serotonin metabolism, and increase the development of different proteins involved in brain serotonin function by increasing levels of tryptophan, the amino acid precursor of serotonin, in blood plasma and cerebrospinal fluid [78]. Increased levels of norepinephrine and its metabolites, as well as activation of tyrosine hydroxylase, an enzyme involved in the synthesis of norepinephrine, are also correlated with chronic exercise [79]. This can be converted into a major exercise-induced reduction in people's depression rating scale ratings, and hence possibly into a reduction in the severity of depressive symptoms in clinical practice [80].

VI. CONCLUSION

Depression is a widespread neurodegenerative disorder. Depression continues to negatively affect the quality of life of individuals. The evidence from the study supports the typical neurobiological and psycho-social meaning of depression. The receptors of serotonin and norepinephrine play an important role in symptoms of depression and there is some clinical evidence that it may be beneficial to prescribe double-acting antidepressants. Glucose is essential energy source of brain metabolism. Decreased brain energy metabolism leads to depression. Lactate has cat as a byproduct in brain energy metabolism through monocarboxylate transporters. Monocarboxylate transporters [MCTs] are a family of transporters, which participate in the facilitated diffusion of lactate as well as the incorporation and release of several other metabolically important monocarboxylates, such as Pyruvate and ketone bodies. To prevent only partial remission of symptoms with unfavourable biological and psycho-social effects, therapy should start early and aggressively. Therefore, the further research is needed to identify effective strategies in lactate content and expression of MCT in animal model.

VII. REFERENCES

[1] Fekadu, N., Shibeshi, W. and Engidawork, E. 2017. Major depressive disorder: pathophysiology and clinical management. *J Depress Anxiety*, *6*(1), pp.255-257.

[2] Mitchell, A.J., Vaze, A. and Rao, S. 2009. Clinical diagnosis of depression in primary care: a meta-analysis. *The Lancet*, 19:374-609

[3] Bromet, E., Andrade, L.H., Hwang, I., Sampson, N.A., Alonso, J., De Girolamo, G., De Graaf, R., Demyttenaere, K., Hu, C., Iwata, N. and Karam, A.N. 2011. Cross-national epidemiology of DSM-IV major depressive episode. *BMC medicine*, *9*(1), pp.1-16.

[4] Whooley, M.A. and Wong, J.M. 2013. Depression and cardiovascular disorders. *Annual review of clinical psychology*, *9*, pp.327-354.

[5] WHO. Suicide. 2016. Available from: https://www.who.int/mental_health/suicide-prevention/myths.pdf?ua=1

[6] Chesney, E., Goodwin, G.M. and Fazel, S. 2014. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World psychiatry*, *13*(2), pp.153-160.

[7] Weizman, S., Gonda, X.E.N.I.A., Dome, P. and Faludi, G. 2012. Pharmacogenetics of antidepressive drugs: a way towards personalized treatment of major depressive disorder. *Neuropsychopharmacol Hung*, *14*(2), pp.87-101.

[8] Langreth and Robert. 2010.Study Undermines Case for Antidepressants. Forbes. Retrieved 2010-07-02.

[9] Lammers, C.H., Diaz, J., Schwartz, J.C. and Sokoloff, P. 2000. Selective increase of dopamine D 3 receptor gene expression as a common effect of chronic antidepressant treatments. *Molecular psychiatry*, *5*(4), pp.378-388.

[10] Hettema, J.M., An, S.S., Neale, M.C., Bukszar, J., Van den Oord, E.J.C.G., Kendler, K.S. and Chen, X. 2006. Association between glutamic acid decarboxylase genes and anxiety disorders, major depression, and neuroticism. *Molecular psychiatry*, *11*(8), pp.752-762.

[11] Dienel, G.A., 2019. Brain glucose metabolism: integration of energetics with function. *Physiological reviews*, *99*(1), pp.949-1045.

[12] Lu, W., Huang, J., Sun, S., Huang, S., Gan, S., Xu, J., Yang, M., Xu, S. and Jiang, X. 2015. Changes in lactate content and monocarboxylate transporter 2 expression in Aβ 25-35-treated rat model of Alzheimer's disease. *Neurological Sciences*, *36*(6), pp.871-876.

[13] Bouzier-Sore, A.K., Voisin, P., Canioni, P., Magistretti, P.J. and Pellerin, L. 2003. Lactate is a preferential oxidative energy substrate over glucose for neurons in culture. *Journal of Cerebral Blood Flow & Metabolism*, *23*(11), pp.1298-1306.

[14] Balmaceda-Aguilera, C., Cortes-Campos, C., Cifuentes, M., Peruzzo, B., Mack, L., Tapia, J.C., Oyarce, K., García, M.A. and Nualart, F. 2012. Glucose transporter 1 and monocarboxylate transporters 1, 2, and 4 localization within the glial cells of shark blood-brain-barriers. *PloS one*, *7*(2), p.e32409.

[15] Bhowmik, D., Kumar, K. S., Srivastava, S., Paswan, S., & Dutta, A. S. 2012. Depression - Symptoms, Causes, Medications and Therapies. *The Pharma Innovation*, 1(3), 37-51.

[16] NIMH. *Depression Basics.* U.S. Department of Health and Human Services National Institutes of Health NIH Publication No. 19-MH-8079 Revised 2016. (2016). p. 1–6. Available at: https://www.nimh.nih.gov/health/publications/depression/index.shtml.

[17] Thomas, E. and Seedat, S. 2018. The diagnosis and management of depression in the era of the DSM-5. *South African Family Practice*, *60*(1).

[18] Grobler, G. 2013. Major depressive disorder: The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders. *South African Journal of Psychiatry*, *19*(3), pp.157-163.

[19] aan het Rot, M., Mathew, S.J. and Charney, D.S. 2009. Neurobiological mechanisms in major depressive disorder. *Cmaj*, *180*(3), pp.305-313.

[20] Price, A.L. and Marzani-Nissen, G.R. 2012. Bipolar disorders: a review. *American family physician*, *85*(5), pp.483-493.

[21] Ayano, G. 2016. Bipolar Disorder: A Concise Overview of Etiology, Epidemiology Diagnosis and Management: Review of Literatures. SOJ Psychol 3 (1): 1-8. *Bipolar Disorder: A Concise Overview of Etiology, Epidemiology Diagnosis and Management: Review of Literatures*.

[22] Holmans, P., Weissman, M.M., Zubenko, G.S., Scheftner, W.A., Crowe, R.R., DePaulo Jr,, MD, J.R., Knowles, J.A., Zubenko, W.N., Murphy-Eberenz, K., Marta, D.H. and Boutelle, S. 2007. Genetics of recurrent early-onset major depression (GenRED): final genome scan report. *American Journal of Psychiatry*, *164*(2), pp.248-258.

[23] Yonkers, K.A., O'Brien, P.S. and Eriksson, E. 2008. Premenstrual syndrome. *The Lancet*, *371*(9619), pp.1200-1210.

[24] Brigitta, B., 2002. Pathophysiology of depression and mechanisms of treatment. *Dialogues in clinical neuroscience*, *4*(1), p.7.

[25] Kandel, E.R. and Squire, L.R. 2000. Neuroscience: Breaking down scientific barriers to the study of brain and mind. *Science*, *290*(5494), pp.1113-1120.

[26] Perez, J., Tardito, D., Mori, S., Racagni, G., Smeraldi, E. and Zanardi, R. 2000. Abnormalities of cAMP signaling in affective disorders: implications for pathophysiology and treatment. *Bipolar disorders*, *2*(1), pp.27-36.

[27] Coppen, A. 1967. The biochemistry of affective disorders. *Br J Psychiatry*, *113*(504), pp.1237-1264.

[28] Kumar, A. and Singh, A., 2015. A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacological reports*, *67*(2), pp.195-203.

[29] Aarsland, D., Påhlhagen, S., Ballard, C.G., Ehrt, U. and Svenningsson, P. 2012. Depression in Parkinson disease—epidemiology, mechanisms and management. *Nature Reviews Neurology*, *8*(1), pp.35-47.

[30] Schmidt, H.D., Shelton, R.C. and Duman, R.S. 2011. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. *Neuropsychopharmacology*, *36*(12), pp.2375-2394.

[31] Pittenger, C. and Duman, R.S. 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology*, *33*(1), pp.88-109.

[32] Lang, U.E., Günther, L., Scheuch, K., Klein, J., Eckhart, S., Hellweg, R., Danker-Hopfe, H. and Oehler, J. 2009. Higher BDNF concentrations in the hippocampus and cortex of an aggressive mouse strain. *Behavioural brain research*, *197*(1), pp.246-249.

[33] Aykaç, A. and Sehirli, A.O. 2020. The role of the SLC transporters protein in the neurodegenerative disorders. *Clinical Psychopharmacology and Neuroscience*, *18*(2), p.174.

[34] Pérez-Escuredo, J., Van Hée, V.F., Sboarina, M., Falces, J., Payen, V.L., Pellerin, L. and Sonveaux, P. 2016. Monocarboxylate transporters in the brain and in cancer. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1863*(10), pp.2481-2497.

[35] Pierre, K. and Pellerin, L. 2005. Monocarboxylate transporters in the central nervous system: distribution, regulation and function. *Journal of neurochemistry*, *94*(1), pp.1-14.

[36] De Heredia, F.P., Wood, I.S. and Trayhurn, P. 2010. Hypoxia stimulates lactate release and modulates monocarboxylate transporter (MCT1, MCT2, and MCT4) expression in human adipocytes. *Pflügers Archiv-European Journal of Physiology*, *459*(3), pp.509-518.

[37] Bélanger, M., Allaman, I. and Magistretti, P.J. 2011. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. *Cell metabolism*, *14*(6), pp.724-738.

[38] Camandola, S. and Mattson, M.P. 2017. Brain metabolism in health, aging, and neurodegeneration. *The EMBO journal*, *36*(11), pp.1474-1492.

[39] Vannucci, R.C. and Vanncci, S.J. 2007. Glucose metabolism in the developing brain. *Semin Perinatal*, 24: 107-115.

[40] Pierre, K. and Pellerin, L. 2005. Monocarboxylate transporters in the central nervous system: distribution, regulation and function. *Journal of neurochemistry*, *94*(1), pp.1-14.

[41] Smith, D.J., Nicholl, B.I., Cullen, B., Martin, D., Ul-Haq, Z., Evans, J., Gill, J.M., Roberts, B., Gallacher, J., Mackay, D. and Hotopf, M. 2013. Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PloS one*, *8*(11), p.e75362.

[42] Jha, M.K. and Morrison, B.M. 2018. Glia-neuron energy metabolism in health and diseases: new insights into the role of nervous system metabolic transporters. *Experimental neurology*, *309*, pp.23-31.

[43] Draoui, N. and Feron, O. 2011. Lactate shuttles at a glance: from physiological paradigms to anti-cancer treatments. *Disease models & mechanisms*, *4*(6), pp.727-732.

[44] Overgaard, M., Rasmussen, P., Bohm, A.M., Seifert, T., Brassard, P., Zaar, M., Homann, P., Evans, K.A., Nielsen, H.B. and Secher, N.H. 2012. Hypoxia and exercise provoke both lactate release and lactate oxidation by the human brain. *The FASEB Journal*, *26*(7), pp.3012-3020.

[45] Todd, J.J. 2014. Lactate: valuable for physical performance and maintenance of brain function during exercise. *Bioscience Horizons: The International Journal of Student Research*, *7*.

[46] Boumezbeur, F., Petersen, K.F., Cline, G.W., Mason, G.F., Behar, K.L., Shulman, G.I. and Rothman, D.L. 2010. The contribution of blood lactate to brain energy metabolism in humans measured by dynamic 13C nuclear magnetic resonance spectroscopy. *Journal of Neuroscience*, *30*(42), pp.13983-13991.

[47] Genc, S., Kurnaz, I.A. and Ozilgen, M. 2011. Astrocyte-neuron lactate shuttle may boost more ATP supply to the neuron under hypoxic conditions-in silico study supported by in vitro expression data. *BMC systems biology*, *5*(1), pp.1-13.

[48] Baltan, S. 2015. Can lactate serve as an energy substrate for axons in good times and in bad, in sickness and in health?. *Metabolic brain disease*, *30*(1), pp.25-30.

[49] Genc, S., Kurnaz, I.A. and Ozilgen, M. 2011. Astrocyte-neuron lactate shuttle may boost more ATP supply to the neuron under hypoxic conditions-in silico study supported by in vitro expression data. *BMC systems biology*, *5*(1), pp.1-13.

[50] Salmasultana, S., Sukumari, P., Shafi, S.K., Maheswari, D., Ramsai, P., Sasikumar, K. and Sravani, P. 2018. Pharmacological Evaluation of Antidepressant Activity of Piper Betel Leaves and Clove. *Int. J. Chem, Pharm, Sci.* 6(4): 126-133

[51] Fasipe, O.J. 2019. The emergence of new antidepressants for clinical use: Agomelatine paradox versus other novel agents. *IBRO reports*, *6*, pp.95-110.

[52] Mittal, R., Debs, L.H., Patel, A.P., Nguyen, D., Patel, K., O'Connor, G., Grati, M.H., Mittal, J., Yan, D., Eshraghi, A.A. and Deo, S.K. 2017. Neurotransmitters: The critical modulators regulating gut–brain axis. *Journal of cellular physiology*, *232*(9), pp.2359-2372.

[53] Ng, C.W.M., How, C.H. and Ng, Y.P. 2017. Managing depression in primary care. *Singapore medical journal*, *58*(8), p.459.

[54] Khushboo, S.B. and Sharma, B., 2017. Antidepressants: mechanism of action, toxicity and possible amelioration. *J. Appl. Biotechnol. Bioeng*, *3*, pp.1-13.

[55] Celada, P., Puig, M.V., Amargós-Bosch, M., Adell, A. and Artigas, F. 2004. The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. *Journal of Psychiatry and Neuroscience*, *29*(4), p.252.

[56] Mourilhe, P. and Stokes, P.E. 1998. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. *Drug Safety*, *18*(1), pp.57-82.

[57] Obata, H. 2017. Analgesic mechanisms of antidepressants for neuropathic pain. *International journal of molecular sciences*, *18*(11), p.2483.

[58] Taylor, C., Fricker, A.D., Devi, L.A. and Gomes, I., 2005. Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. *Cellular signalling*, *17*(5), pp.549-557.

[59] Barts, L.T. and Greenblatt ,D. J. 2011. Clinical pharmacology and therapeutics of antidepressants. Pharmacotherapy of Depression. USA: *Springer Science & Business Media*, 33–124.

[60] Möller, H.J. and Volz, H.P. 1996. Drug treatment of depression in the 1990s. *Drugs*, *52*(5), pp.625-638.

[61] Goodwin, G.M. and Malhi, G.S. 2007. What is a mood stabilizer?. *Psychological medicine*, *37*(5), pp.609-614.

[62] Schloesser, R.J., Martinowich, K. and Manji, H.K. 2012. Mood-stabilizing drugs: mechanisms of action. *Trends in neurosciences*, *35*(1), pp.36-46.

[63] Vieta, E., Günther, O., Locklear, J., Ekman, M., Miltenburger, C., Chatterton, M.L., Åström, M. and Paulsson, B. 2011. Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. *International Journal of Neuropsychopharmacology*, *14*(8), pp.1029-1049.

[64] Sundsted, K.K., Burton, M.C., Shah, R. and Lapid, M.I. 2014. Preanesthesia medical evaluation for electroconvulsive therapy: a review of the literature. *The journal of ECT*, *30*(1), pp.35-42.

[65] Baghai, T.C. and Möller, H.J. 2008. Electroconvulsive therapy and its different indications. *Dialogues in clinical neuroscience*, *10*(1), p.105.

[66] Segi-Nishida, E. 2011. Exploration of new molecular mechanisms for antidepressant actions of electroconvulsive seizure. *Biological and Pharmaceutical Bulletin*, *34*(7), pp.939-944.

[67] Rosenquist, P.B., Miller, B. and Pillai, A. 2014. The antipsychotic effects of ECT: a review of possible mechanisms. *The journal of ECT*, *30*(2), pp.125-131.

[68] Baldinger, P., Lotan, A., Frey, R., Kasper, S., Lerer, B. and Lanzenberger, R. 2014. Neurotransmitters and electroconvulsive therapy. *The journal of ECT*, *30*(2), pp.116-121.

[69] Cuijpers, P., Andersson ,G., Donker, T. and van Straten, A. 2011. Psychological treatment of depression: Results of a series of meta-analyses. *Nord J Psychiatry*, Early Online, 1–11.

[70] Ambresin, G., Despland, J.N., Preisig, M. and de Roten, Y. 2012. Efficacy of an adjunctive brief psychodynamic psychotherapy to usual inpatient treatment of depression: rationale and design of a randomized controlled trial. *BMC psychiatry*, *12*(1), pp.1-9.

[71] Sirey, J.A., Bruce, M.L. and Kales, H.C.,2010. Improving antidepressant adherence and depression outcomes in primary care: the treatment initiation and participation (TIP) program. *The American Journal of Geriatric Psychiatry*, *18*(6), pp.554-562.

[72] Black Dog Institute. Treatment of depression. 2012. Fact sheet. 1-4.

[73] Buchanan, R.D. and Haslam, N. 2019. Psychotherapy in The Cambridge Handbook of the Intellectual History of Psychology, Cambridge: Cambridge University *Press*, pp.468-494.

[74] Sani, S.H.Z., Fathirezaie, Z., Brand, S., Pühse, U., Holsboer-Trachsler, E., Gerber, M. and Talepasand, S. 2016. Physical activity and self-esteem: testing direct and indirect relationships associated with psychological and physical mechanisms. *Neuropsychiatric Disease and Treatment*, *12*, p.2617.

[75] Blake, H. 2012. Physical activity and exercise in the treatment of depression. *Front. Psychiatry*, 3(106):1-4.

[76] Lawlor, D.A. and Hopker, S.W., 2001. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *Bmj*, *322*(7289), p.763.

[77] Helmich, I., Latini, A., Sigwalt, A., Carta, M.G., Machado, S., Velasques, B., Ribeiro, P. and Budde, H. 2010. Neurobiological Alterations Induced by Exercise and Their Impact on Depressive Disorders. *Clinical Practice & Epidemiology in Mental Health*, 6:115-125.

[78] Young, S.N. 2007. How to increase serotonin in the human brain without drugs. *Journal of psychiatry & neuroscience: JPN*, *32*(6), p.394.

[79] Lin, T.W. and Kuo, Y.M. 2013. Exercise benefits brain function: the monoamine connection. *Brain sciences*, *3*(1), pp.39-53.

[80] Slavich, G.M. and Irwin, M.R. 2014. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin*, *140*(3), p.774.